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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,615	11/21/2003	Gregor Meyers	0652.1900001/EKS/J-H	8199

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EXAMINER	
ZEMAN, ROBERT A	
ART UNIT	PAPER NUMBER
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/19/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/717,615	MEYERS, GREGOR	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-28 and 62-92* is/are pending in the application.

4a) Of the above claim(s) *24-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/325,542.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9-28-2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on 3-10-2005 is acknowledged. Claim 24 has been amended. Claims 1-16, 18-23, 29-33, 35-44 and 53-61 have been canceled. Claims 62-92 have been added.

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on 3-10-2005 is acknowledged. Claims 24-28 and 62-92 are pending. Claims 24-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 62-92 are currently under examination.

Information Disclosure Statement

The Information Disclosure Statement filed on 9-28-2005 has been considered. An initialed copy is attached hereto.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 62-92 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 68-116 of U.S. Patent No. 09/325,542. Although the conflicting claims are not identical, they are not patentably distinct from each other because both set claims are drawn to pestiviruses wherein the RNase activity of glycoprotein E^{RNS} is inactivated by a mutation of at least one amino acid of said glycoprotein with proviso that when the pestivirus is the CSFV pestivirus, the amino acid at position 297 or 346 of SEQ ID NO:34 is not lysine. The instant claims differ from those of the copending application in that they are drawn to vaccine compositions. It should be noted that the limitation "vaccine" is deemed an intended use and as such does not make the compositions of the instant claims patentable over the compositions of the copending application.

Claim Rejections - 35 USC § 112, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001.

Claims 62-92 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the claimed invention.

The specification lists 26 mutants with various mutations and/or deletions in amino acid positions 295-307 and 340-351 (not the 338-357 range recited in the claims) of SEQ 10 NO:34. The mutations consisted of single or multiple deletions and/or mutations in either one or both of the aforementioned amino acid ranges (See Table I on page 21). Of the 26 mutants disclosed only 11 were viable and could be considered candidates for a vaccine. However, only one mutant, C-346-d, was tested for efficacy as a vaccine. The C-346-d mutant differs from the wild-type protein in that it has the Histidine residue at amino acid position 346 deleted. Said mutant was viable and the RNase activity of the E^{RNS} glycoprotein had been ablated. The specification discloses many animal studies showing that the C-346-d mutant provided protective immunity to pestiviruses CSFV and BVOV. However, none of the other viable mutants were used in any animal studies. People of skill in the art require documented evidence that a benefit (protective immunity) can be derived by the therapeutic application of a given substance (vaccine); however, a survey of the relevant art does not indicate that vaccines claimed (other than those derived from the deletion of the Histidine residue at position 346) provide such benefit.

The instant claims are drawn to methods of utilizing "live vaccines" to protect an animal against a disease caused by an infectious organism. With the exception of the C-346-d mutant, the specification fails to disclose a single BVDV or CSFV pestivirus that is effective as a vaccine against any given disease (or even a infection by its component pathogen). The aforementioned claims are directed to encompass all infectious organisms. Only the C-346-d mutant meets the written description provision of 35 USC 112, first paragraph since the specification is silent as to what "phenotype" is required for a given microbe to be an effective live vaccine or whether there is a correlation

between phenotype and efficacy as a vaccine. Additionally, the claims are drawn to a vast genus of vaccines. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that **Applicant has possession the claimed invention**. To adequately describe the genus of vaccines, Applicant must adequately describe the antigenic determinants (immunoepitopes) that elicit a protective immune response.

However, the specification does not disclose distinguishing and identifying features of a representative number of members of the genus of vaccines to which the claims are drawn, such as a correlation between the structure of the immunoepitope its recited function (to elicit an protective immune response), so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of vaccines.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal

Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written

description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan et al. (*Nature Biotechnology* **7**: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of immunoepitopes, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of vaccines. Moreover, the specification is silent with regard to what "chemotherapeutic agents" would have efficacy against a given infectious organism; what constitutes a life cycle and/or infectious cycle of a given infectious organism or how said cycles are measured *in vivo.* Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of immunoepitopes (antigenic determinants) is not deemed representative of the genus of vaccines to which the claims refer. Consequently, only the C-346-d mutant meets the written description provision of 35 USC 112, first paragraph.

Enablement

Claims 62-92 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a live pestivirus vaccine wherein the RNase activity of the glycoprotein E^{RNS} is inactivated by the **deletion** of the Histidine residue at amino acid position 346 of SEQ 10 NO:34 (Figure I), does not reasonably provide enablement for a live pestivirus vaccine in which the RNase activity of the E^{RNS} glycoprotein is inactivated by the mutation of the Histidine at amino acid position 346 or the deletion and/or mutation of any of the residues in amino acid positions 295-357. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejected claims are drawn to the prophylactic use of infectious organisms and chemotherapeutic agents against unnamed diseases. To be a prophylactic composition, the composition must elicit protective immunity, demonstrable by pathogen challenge experiments in a reasonable model system. The specification discloses methods, and hence is enabling, for making pestivirus mutants where the RNase activity of the E^{RNS} glycoprotein has been inactivated by either amino acid substitution and/or deletion. The specification lists 26 mutants with various mutations and/or deletions in amino acid positions 295-307 and 340-351 (not the 338-357 range recited in the claims) of SEQ 10 NO:34. The mutations consisted of single or multiple deletions and/or mutations in either one or both of the aforementioned amino acid ranges (See Table I on page 21). Of the 26 mutants disclosed only 11 were viable and could be considered candidates for a vaccine. However, only one mutant, C-346-d, was tested for efficacy as a vaccine. The C-346-d mutant differs from the wild-type protein in that it has the Histidine residue at amino acid position 346 deleted. Said mutant was viable and the RNase activity of the E^{RNS} glycoprotein had been ablated. The specification discloses many animal

studies showing that the C-346-d mutant provided protective immunity to pestiviruses CSFV and BVOV. However, none of the other viable mutants were used in any animal studies. People of skill in the art require documented evidence that a benefit (protective immunity) can be derived by the therapeutic application of a given substance (vaccine); however, a survey of the relevant art does not indicate that vaccines claimed (other than those derived from the deletion of the Histidine residue at position 346) provide such benefit. The specification fails to disclose any other pestivirus capable of inducing a protective immune response against a given disease. The specification is silent as to what "phenotype" is required for a given infectious organism to be an effective vaccine against a given malady or whether there is a correlation between phenotype and efficacy as a vaccine. Additionally, Applicant has failed to demonstrate any given "antigenic determinant" is capable of eliciting a protective immune response against a given infectious organism. While the skill in the art of immunology is high, to date, prediction of protective immunity for any given composition in any given animal is quite unpredictable. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome **and form immunoepitopes**. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid

substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally, as evidenced by Greenspan et al. (*Nature Biotechnology* 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. This constitutes undue experimentation. Therefore, given the lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the generation of protective immunity, the specification, as filed, does not provide enablement for any live vaccine other than the C-346-d pestivirus mutant.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 62-92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 62-92 are rendered vague and indefinite by the use of the term "vaccine". It is unclear against what specific "pathogen" the claimed compositions are supposed elicit a protective immune response.

Claim 85 is vague and indefinite as it is dependent on itself. Consequently, it is impossible to determine the metes and bounds of the claimed invention.

Claims 90-92 are rendered vague and indefinite by the use of the phrase "for inducing an immunological response in an animal". It is unclear to what Applicant is referring to as a "vaccine" would necessarily induce an immune response (i.e. induce protective immunity).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272 0866. The examiner can normally be reached on 7:30 am - 5:30 pm Monday - Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272 0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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ROBERT A. ZEMAN
PRIMARY EXAMINER

December 6, 2006